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DATE: 5/15/02

ATTENTION: GAIL HERMAN

FAX#: 685-9452

FROM: RODNEY HO

Page 1 of 14 page(s).

EXHIBIT 3

UNIVERSITY OF WASHINGTON

Office of Technology Transfer

March 28, 2000

To: Rodney J.Y. Ho
Pharmaceutics
Box 357610

Che-Chung Tsai
U.W. Primate Center
Box 357330

From: Karen L. Deyerle, PhD Janice Walsh for
Manager of Technology Transfer
for the Health Sciences, Box 354810

Subject: Co-inventor's assignment of invention(s) - A novel strategy to target anti-HIV drugs to lymphnodes and lymphoid cells -
OTT Ref#2606-3342

As provided by the University's Patent and Invention policy, Vol 4, Part 5, Section 7 of the University Handbook, the University requests title to the above referenced invention disclosed by you to the Office of Technology Transfer. Transfer of title from you to the University serves as the basis for the University to commit its resources towards further evaluation of the invention so that the technology may be successfully transferred. As an inventor, you will share in any net income which might accrue from licensing this technology.

I have enclosed an Assignment form. Please execute it before a notary public and return it to me at the Office of Technology Transfer. (A notary public is also available at OTT). If you have any questions or concerns please feel free to call me at (206) 543-3970.

Enclosure: Assignment form

KLD:jcw

1107 NE 45th Street, Suite 200 Seattle, Washington 98105-4631 (206) 543-3970 FAX: (206) 685-4767 Campus mail: Box 354810

UW

UNIVERSITY OF WASHINGTON

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March 28, 2000

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Co-Inventor's ASSIGNMENT of INVENTION(S) to the University of Washington

WHEREAS, I, Rodney J.Y. Ho (hereinafter referred to as ASSIGNOR) having a post office address of 15812 35th Avenue N.E. Seattle, WA 98155, am a co-inventor in the INVENTION(S) referred to as "A novel strategy to target anti-HIV drugs to lymphnodes and lymphoid cells" as described in a disclosure submitted to the University of Washington on March 23, 2000 and assigned an Office of Technology Transfer (OTT) file Number of 3342 and whereas this Assignment is intended to cover the INVENTION(S) identified in that disclosure as developed by us at the University of Washington, as a product of our research at the University of Washington;

WHEREAS, the UNIVERSITY OF WASHINGTON, (hereinafter referred to as ASSIGNEE), a public institution of higher education having a place of business at Seattle, Washington is desirous of acquiring the ASSIGNORS' entire right, title and interest in and to the INVENTION(S) and in and to any letters patent that may be granted therefor in the United States and in any and all foreign countries;

NOW, THEREFORE, for sufficient, good and valuable consideration, the receipt of which is hereby acknowledged, ASSIGNOR hereby sells, assigns and transfers unto ASSIGNEE the ASSIGNOR'S entire right and title to and interest in said application and said INVENTION(S) for the United States of America and its territorial possessions and all foreign countries, and the ASSIGNOR'S entire right, title and interest in and to any and all letters patents which may be granted therefor in the United States of America and its territorial possessions and in any and all foreign countries, and in any and all divisions, reissues and continuations thereof, including the right to claim priority rights deriving from said United States application by virtue of the International Convention, said INVENTION(S) and all applications and patents on said INVENTION(S) to be held and enjoyed by ASSIGNEE as entirely as the same would have been held and enjoyed by ASSIGNORS had this sale, assignment and transfer not been made. ASSIGNOR hereby authorizes and requests the Commissioner of Patents and Trademarks to issue all letters patent(s) on said INVENTION(S) to ASSIGNEE. ASSIGNOR hereby further agrees and promises to execute all instruments and render all such assistance as ASSIGNEE may request in order to make and prosecute any and all applications on said INVENTION(S), to enforce any and all patents on said INVENTION(S), and to confirm in ASSIGNEE legal title to said INVENTION(S) and all applications and patents on said INVENTION(S), all without charge to ASSIGNEE but at no expense to ASSIGNOR.

Rodney J.Y. Ho

April 5, 2000
Date

STATE OF WASHINGTON)
) ss
County of King)

On this 5th day of April 2000, Rodney J.Y. Ho personally appeared before me and executed the foregoing document.

Notary Public in and for the State of Washington

Residing at: 4821 210th Ct NE Redmond WA 98053

My Commission expires: March 28, 2004

CATHERINE J. JOHNSON NOTARY PUBLIC MARCH 28, 2004 STATE OF WASHINGTON

Disclosure #:_____

University of Washington
INVENTION DISCLOSURE SUPPLEMENT
(FORM ID-2)

The information requested on this form documents the development history of an invention previously disclosed to the Office of Technology Transfer. This information is necessary for the University to evaluate the invention for possible patent rights and commercial applications. **Please complete both sides of the form. Attach additional documents as needed.**

Project Number (Include if you've been assigned an OTT Project Number)_____

1. Invention History. Where a date is not well documented, indicate that the date is approximate using a phrase such as "on or about" or give a span of time in which the event took place. For locations on campus, use "UW"; for others, provide the name of city and state.

Stage of Inventive Activity	Date	Location
Initial idea (conception)	3/1999	H272H
First verbal description (public or private) to others	6/1999	H272H
Invention development records, notes, drawings (evidence of diligence)	7/1999	H264
First description of complete invention, oral or written (first constructive reduction to practice)	8/1999	H264
Any sale or public use of the invention in the United States		

Note: "Sale" means (generally) "on sale," including any offer to sell or any actual sale to a purchaser, whether or not such "sale" activity was secret or non-secret. "Public Use" means (generally) use of the invention by the inventor in public, or used by the public. Other secret or non-secret uses of the invention by other than the inventor may also qualify as public use.

2. CV and External Funding. Provide a current copy of each inventor's CV (listing all papers each inventor has authored or co-authored). List and provide **copies of any funded or unfunded grant proposals** related to the invention, and state the funding status for each.

HL56548
AI31854

3. Publications. List any reports, abstracts, papers, or theses related to the invention that have been published or are in preparation. Include **two complete copies of the first publication that describes the invention, and provide date of publication or intended publication.**

See the attached proposal submitted in confidence to NIH for funding

4. References. List any references, issued patents, patent applications, review articles, or other publications that pertain to the invention. Include copies if available.

5. Key Words (for on-line patent and literature searches).

anti-HIV drug/ lymph node targeting/ lipid drug interactions / high degree of dissociation

Please notify OTT if you become aware of any additional publications, patents, or other references pertaining to the invention.

(continued on reverse)

6. **Inventors.** Include those individuals who have made creative contributions to the invention. For patents, determination of inventors depends on the particulars of the invention specification and allowed claims in the invention as described in the parent application.

Signature 3/16/2002 Date	Signature Date
Rodney J.Y. Ho Legal Name (Print)	Che-Chung Tsai Legal Name (Print)
Associate Professor Title	Pathologist Title
H 272-H, Health Sciences Complex Address (Office)	I- 039 Address (Office)
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Citizenship USA	Citizenship USA
Signature Date	Signature Date
Legal Name (Print)	Legal Name (Print)
Title	Title
Address (Office)	Address (Office)
Address (Home)	Address (Home)
Phone: Work Home	Phone: Work Home
Social Security No.	Social Security No.
Citizenship	Citizenship

Please notify OTT of any subsequent change of address or telephone number(s).

2606-3342DL

University of Washington
INVENTION DISCLOSURE (FORM ID-1)

Use this form to disclose inventions to the University's Office of Technology Transfer, Box 354810. Prompt disclosure allows the University to secure intellectual property rights as appropriate and to fulfill obligations it may have to external sponsors of research.

Project Number (Include if you have been assigned an OTT project number) _____

1. Title of Invention

A novel strategy to target anti-HIV drugs to lymphnodes and lymphoid cells

2. Description (briefly describe general nature, primary functions, and areas of principal use)

The goal of this invention is to improve our ability to reduce virus found in latent reservoirs. Using lipid-drug complexes of about 50 nm, we were able to achieve selective accumulation of an anti-HIV drug in lymph nodes.

3. Funding Source(s) Was work leading to the invention supported by:

A. Internal allocations from:
- Graduate School Fund? Yes ___ No X
- Royalty Research Fund? Yes ___ No X
- Washington Technology Center? Yes ___ No X

Project Title Kinetics and Mechanisms of Mother to Fetus HIV Transmission

B. Federal and/or External Grant or Contract awards: Yes X No ___

Grant/Contract #s HL 56548 + AI 31854 + AI 52663 (per R. Ho P&R, Ho 8/2/04) 8/2/04

4. Government Employee(s) Please list any inventors associated with the V.A. Medical Center.

Rodney J.Y. Ho, Ph.D.

5. Principal Developer(s)

Signature _____ Title Associate Professor

Printed Name Rodney J.Y. Ho Dept Pharmaceutics

Date 3/14/2000 Mail Stop 357610 Work Phone 685-3914

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Social Security No 546-49-6363 Citizenship U.S.A.

Signature _____ Title Pathologist

Printed Name Che-Chung Tsai Dept U.W. Primate Center

Date 3-17-2000 Mail Stop 357330 Phone 206) 221-3156

Home Address 207-7th Street, Cheney, WA 99004 Home Phone 206-545-7562

Social Security No _____ Citizenship USA

OTT Date Received: OTT Disclosure Number Assigned:

rev 09-93

A novel strategy to enhance anti-HIV drug accumulation to lymphoid tissues and cells

I. Specific Aims

The long-term goal of this program is to develop a mean to reduce HIV found in latent reservoirs. While the additional reservoirs outside of lymphatic are remained elusive, it is clear that a significant fraction of latent virus is found in visceral (e.g., mesentery) lymph nodes, in addition to peripheral nodes that can be readily accessed by biopsy procedures in humans. The use of HIV or SIV infected primate will provide a mean to systematically evaluate drug and virus concentrations simultaneously at both peripheral and visceral (i.e., mesentery) nodes in an attempt to correlate drug concentration in tissue to virus load. The use of lipid associated drug complexes to achieve higher concentration of drugs in lymph nodes would allow us to discern whether increasing local drug concentration would further reduce the virus load in the latent reservoir.
Hence, with SIV or HIV-2- infected macaques and indinavir as a model anti-HIV drug, the specific aims of this proposal are designed to test the following hypotheses

Hypothesis 1: Drug concentrations in lymph nodes can be enhanced by delivery of a model drug, indinavir in lipid-associated form, in comparison to free drug formulation.

Hypothesis 2: Enhanced drug accumulation in lymph nodes further reduces the seemingly constant virus load in lymphoid tissues achieved with free drug administration.

II. Background

HIV infection continues to be a major health problem in the United States. A number of anti-HIV drug combinations (often referred to as HAART, highly active anti-retroviral therapy) that attack the virus by mechanisms including inhibition of reverse transcriptases (selective for either nucleoside or no-nucleoside), and viral proteases have maximally decreased the virus concentration in blood of HIV infected patients on chronic therapy. However, a significant proportion of virus in the HIV infected individuals are found in lymphoid tissues and the HIV concentration in blood do not predict the virus concentration in lymphoid tissues. Data from recent reports (Hockett et al., 1999 J exp med 189, 1545; Pantaleo et al.,1993 Nature 362:255; Pantaleo et al., 1991 Pro Natl Acad Sci USA 88:9838) demonstrated that viral RNA concentrations in lymph nodes remained

relatively constant over the course of HAART in HIV infected patients, despite the low or undetectable levels of HIV in blood or plasma. These data suggest that either the virus found the lymph nodes are resistant to the drug therapy or insufficient exposure of drug to this tissue. However viruses isolated from lymphoid tissues and plasma are equally sensitive to anti-HIV drugs, suggesting the possibility that insufficient drug exposure to lymphoid tissue and cell may be the key to eliminate residual viruses. Therefore, if one can devise a strategy to improve delivery of drugs to lymph nodes at higher concentrations for longer duration, it is likely that virus concentration in lymph node can be greatly reduced.

We have taken a novel approach to a drug carrier design that will likely increase delivery of anti-HIV drug to lymph nodes at higher concentrations for a prolonged period. Lipid-drug particles of 50-80 nm in diameter that are stable in biologic fluid may enhance drug localization in cells and tissues of lymph nodes. While dendritic cells are less efficient than macrophages in particle uptake, both of these cells, considered to be sanctuary of HIV, can uptake the small lipidic particles more efficiently than fluid uptake or pinocytosis. Lipid vesicles or liposomes, with spherical shaped enclosed lipid bilayers with a 50 nm to several micro meters in diameters size have been used successfully to enhance delivery of highly potent anti-fugal and anti-tumor drugs. When small liposomes of about 50-80 nm are given by either IM or SC route or directly injected into the lymphatics, the small liposomes are distributed first into lymphatic, and subsequently, a significant of them are trapped at the draining lymph nodes (Kim and Han 1995, J Microencap 12:437; Hirnle 1997 Hybridoma 16:127). If one can either encapsulate or incorporate an anti-HIV drug into lipid (or liposome) bilayers with high efficiency and stability, the lipid associated drugs can be delivered to lymph nodes with great efficiency in vivo. This will overcome insufficient anti-HIV drug exposure in lymph nodes in clearing the virus dwell in lymph nodes.

In search of the model drug to be tested, we found that anti-HIV drug indinavir would be an ideal drug for incorporating it into lipid bilayer of liposomes at neutral pH (pH=7) for targeting it to lymph nodes. Indinavir exhibit a low aqueous solubility (but high lipid solubility) at pH 7, and a high aqueous solubility at pH 3.0. (The currently available oral indinavir dosage form is formulated with citrate buffer to achieve pH value around 3 to enhance solubility of indinavir for gut absroption). Membrane associated drug will provide the stability of the lipid-drug complex in biological milieu before accumulating in the lymph nodes. As a result, the liposomes loaded with drug molecules can be either taken up by the lymphoid cells and/or provide sustained presence of drug as liposome are gradually metabolized by the lipases found at cell surfaces within lymphoid tissues. This approach may (1) provide much higher concentration of drugs in lymph

nodes that cannot be achieved with free drug administration, and (2) increase intracellular concentration of drug in cells of lymph nodes and systemic circulation for the HIV infected cells that uptake 50-80nm particles. As a result, this strategy may likely to further reduce HIV replication in lymphoid tissues.

III. Preliminary Studies

Effect of pH on the ability of indinavir to associate to lipid bilayer

Using indinavir with about 1000 fold decrease in aqueous solubility differences between pH 3 and pH7 (Lin et al. 1995 Drug Metabolism and Disposition 23:730), we determined the effect of pH on the ability of liposomes to encapsulate or incorporate the drug. At lipid-to-drug ratio of 5:1 (m/m), practically all (80-90%) the drugs in the preparation were found to be associated with liposome at pH-7 (Figure 1). At lower pH value (i.e., 3) where aqueous solubility of drug is higher, we found much lower degree (<30%) of drug incorporated into liposomes. Since the physiological pH value is 7.4 and biological fluids are highly buffered, these lipid-associated drugs are expected to remain stable. Hence, we use the lipid-indinavir complex formed and maintained at pH 7 for the subsequent pharmacokinetic study.

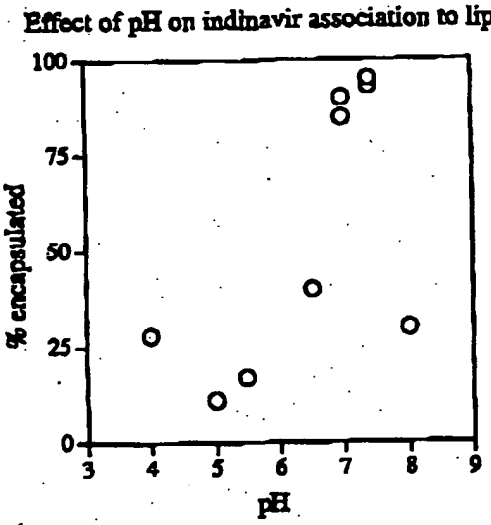

Figure 1: Effects of pH on incorporation of indinavir to liposomes. With lipids containing phosphatidyl choline (egg) : cholesterol (3:1,m/m) and lipid to indinavir 5:1 (m/m), small unilamellar liposomes were prepared with buffer at indicated pH value. They were sonicated to achieve 50-80 nm in diameter. Subsequently, the % lipid-association was determined by separating free from lipid-associated drug by size-exclusion column chromatography. Data expressed were mean of duplicates preparations for indicated pH value.